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(54) Title: PROSTAGLANDIN BASED COMPOSITIONS AND METHOD OF USE THEREOF

(57) Abstract: The present disclosure sets forth particular prostaglandin based compounds that are relatively more stable in aqueous environments than other such compounds; and further that by complexing such a prostaglandin based compound of the disclosure with an agent, such as cyclodextrin, the prostaglandin based compound may be stabilized and provided in a cosmetic composition that can be used to enhance the appearance of hair.

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## **PROSTAGLANDIN BASED COMPOSITIONS AND METHOD OF USE THEREOF**

### **Cross-Referenced to Related Applications**

[001] This application claims the benefit under 35 U.S.C. Section 119(e) of a provisional application U.S. Serial No. 61/127,686, filed on May 14, 2008 and entitled "PROSTAGLANDIN BASED COMPOSITION AND METHOD OF USE THEREOF" which is incorporated by reference herein in its entirety.

### **Field of the Disclosure**

[002] The disclosure relates to a process and composition for enhancing the appearance of one or more properties associated with hair follicles in a subject, such as luster, sheen, brilliance, gloss, glow, shine, patina, length, thickness, density, or overall appearance of the hair using a prostaglandin based compound, such as a prostaglandin, prostamide, and/or a derivative or analog thereof, alone or in association with a stabilizing agent, and/or with a topical cosmetic carrier.

### **Background of the Disclosure**

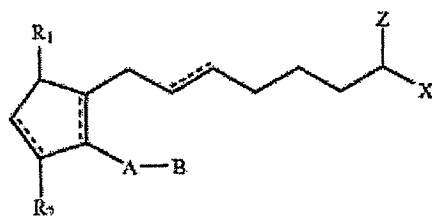
[003] Prostaglandin based compounds, such as prostaglandins, prostamides, as well as their derivative and analogs, have been reported to be useful for enhancing the appearance of hair. However, many prostaglandin based compounds are unstable, and this instability can undermine their effectiveness. For instance, prostaglandin E is unstable in aqueous environments and decomposes to Prostaglandin A and Prostaglandin B.

### **Summary of the Disclosure**

[004] The present disclosure is based, in part, upon the discovery that specific prostaglandin based compounds are relatively more stable in aqueous environments than others; and further that by complexing a prostaglandin based compound of the disclosure with a stabilizing agent, such as cyclodextrin, the prostaglandin may be

stabilized and provided in a cosmetic composition that can be used to enhance the appearance of hair, such as the hair of the eyelashes, eye-brows, and head.

[005] In certain aspects, the disclosure is directed to a topical composition, such as a composition that is intended for application to mammalian skin. For instance, in certain embodiments, a composition of the disclosure is formulated so as to be applied to skin and or hair comprising the eyebrow or eyelash. The composition may include one or more of an effective amount of a prostaglandin based compound; a stabilizing agent; and optionally, a biologically acceptable carrier. In some embodiments, the prostaglandin based compound includes the following structure:



wherein the dashed bonds represent a single or double bond which can be in the cis or trans configuration;

[006] A is an alkylene or alkenylene radical having from two to six carbon atoms, which radical may be interrupted by one or more oxa radicals and substituted with one or more hydroxy, oxo, alkyloxy or alkylcarboxy groups wherein said alkyl radical comprises from one to six carbon atoms;

[007] B is a cycloalkyl radical having from three to seven carbon atoms, or an aryl radical, selected from the group consisting of hydrocarbyl aryl and heteroaryl radicals having from four to ten carbon atoms wherein the heteroatom is selected from the group consisting of nitrogen, oxygen and sulfur atoms;

X is either  $-N(H)CH(CH_2OH)_2$  or  $-OCH(CH_2OH)_2$ ;

Z is  $=O$ ;

one of  $R_1$  and  $R_2$  is  $=O$ ,  $-OH$  or a  $-O(CO)R_3$  group, and the other one is  $-OH$  or  $-O(CO)R_3$ , or  $R_1$  is  $=O$  and  $R_2$  is  $H$ , wherein  $R_3$  is a saturated or unsaturated acyclic hydrocarbon group having from 1 to about 20 carbon atoms, or  $-(CH_2)_mR_4$  wherein  $m$  is 0 or an integer of from 1 to 10, and  $R_4$  is cycloalkyl radical, having from three to

seven carbon atoms, or a hydrocarbyl aryl or heteroaryl radical, as defined above, or a pharmacologically acceptable acid addition salt thereof.

[008] In certain aspects, the disclosure is directed to a method of using a topical composition such as that disclosed herein for the purpose of enhancing the appearance of one or more properties associated with hair follicles in a subject, such as luster, sheen, brilliance, gloss, glow, shine, patina, length, thickness, density, or overall appearance of the hair. In such an instance, a composition of the disclosure may be contacted with the hair and or skin, e.g., which skin may be associated with the hair of a user, in such a manner that the active agent(s) of the composition is capable of penetrating into the skin. In certain embodiments, a method of the disclosure includes contacting the skin and/or hair of the eyelids, eyelashes, eyebrows, crown, arms, legs, etc. with a composition of the disclosure.

[009] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In the case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

[010] Other features and advantages of the invention will be apparent from the following detailed description and claims.

### **Detailed Description of the Invention**

[011] Prostaglandins are lipid compounds derived from cyclic fatty acids, e.g., prostanoic acid. Prostaglandins and prostamides are structurally related small molecules that modulate cellular activities through various cell surface receptors. Typically, both prostaglandins and prostamides contain at least a 20 carbon atom backbone, which backbone includes a 5-carbon (cyclopentane) ring. There are several main types of prostaglandins (PG): PG A, PG B, PGC, PGD, PGE, PGF, PGH, and

PGI, based on the structure of the cyclopentane ring. The naturally occurring prostaglandins are types E, F, A, and B, with PGA and PGB being oxidation products of PGE and PGF.

- [012] Many cells of the body have specific receptors for PG types E and F, and thus, there are a large number of cells of the body that are responsive to PGE and F, whereas the number of cells of the body that have receptors responsive to PGA and/or PGB are comparatively much lower. Accordingly, PGE and PGF are much more active than their derivatives PGA and PGB.
- [013] Prostamides differ from prostaglandins in that with respect to prostaglandins the 1-position comprises a carboxylic acid, and with respect to prostamides, the 1-position comprises an amide group. Further, it has been determined that prostamides exert their effects through receptors that are distinct from prostaglandins, and thus, are biologically distinct there from. See: "Prostamide Antagonist," Woodward et al., Dept. of Biological Sciences, Allergan, Inc.
- [014] Prostaglandins, prostamides, derivatives and analogs thereof, are known to produce a variety of effects. For example, prostaglandin analogs of PGF<sub>2</sub> $\alpha$  and PGE<sub>2</sub> are known to effectuate at least the appearance of hair growth in mammals. See, for instance, Sasaki et al., *Exp. Dermatol.* (2005) May; 14(5):323-8 and Colombe et al., *Exp. Dermatol.* (2007) Sep; 16(9):762-9. In fact, US Patent No. 6,262,105 to Johnstone is directed to the use of a prostaglandin F compound, and US Patent No. 7,351,404 is directed to the use of various particular prostamide compounds, the use of which compounds in cosmetic formulations purportedly stimulates hair growth.
- [015] However, prostaglandins and prostamides, as well as the derivatives and analogs thereof, are unstable in aqueous environments. For instance, in aqueous environments, PGEs and PGFs readily decompose into their less active PGA and PGB derivatives. Specifically, the E and F type prostaglandins possess a hydroxyl group at C11 of the cyclopentene ring, which in the presence of water is readily dehydrated, thereby forming a double bond within the pentene ring indicative of the PGA and PGB types. Accordingly, in order to maximize the effectiveness of such compounds in cosmetic compositions for increasing the appearance of hair growth, a prostaglandin/prostamide composition should be formulated in such a manner so as to

prevent or at least reduce the decomposition of the particular prostaglandin and/or prostamide employed as the active ingredient of the cosmetic composition.

- [016] To prevent the rapid decomposition of prostaglandins, prostamides, their derivatives and analogs, the use of various stabilizers has been proposed, which stabilizers when formulated with various prostaglandins purportedly function to protect the prostaglandin from decomposition. For instance, various prostaglandins have been formulated in conjunction with cyclodextrin so as to increase the stability of the prostaglandin in solution. See, for instance, Gonzales, et al. J. Clin. Pharmacol. (2007) Jan;47(1):121-6, as well as Wiese et al., J. Pharm. Sciences 80:153-156 (1991); Szejtli, J., "Industrial Applications of Cyclodextrins," Inclusion Compounds III, Academic Press, London, England (1984), pp. 355-368.
- [017] Specifically, it was postulated that a portion of the prostaglandin was capable of being inserted within the hydrophobic cavity of the cyclodextrin so as to form an inclusion product therewith. See, for instance, Gu, et al. (2004) Sep;39(9):742-6. However, despite the combination of prostaglandins with stabilizers, such as cyclodextrin, the decomposition of prostaglandin based active agents in solution remains problematic. Without being bound to theory, it is believed with respect to cyclodextrin, that due in part to the long, stretched out structure of the typical prostaglandin like backbone and also due in part to the hydrophilic nature of the carboxyl group at the 1-position, prostaglandins, generally, and some prostamides, are not particularly well suited for forming an inclusion product with cyclodextrins.
- [018] Accordingly, as will be described in greater detail herein below, the present inventors have determined that the prostaglandin based compounds of the present disclosure are more stable in aqueous environments, and in instances wherein the prostaglandin based compounds are combined with stabilizer, such as cyclodextrin, are more suited for forming inclusion products therewith than other such compounds heretofore known and used in cosmetic formulations. Additionally, the present inventors have determined that the prostaglandin based compounds of the present disclosure are capable of increasing the appearance of one or more hair properties such as luster, sheen, brilliance, gloss, glow, shine, patina, length, thickness, density, and/or overall appearance. Therefore, the prostaglandin based compounds of the disclosure, as well as their derivatives and analogs, are useful in cosmetic compositions, particularly

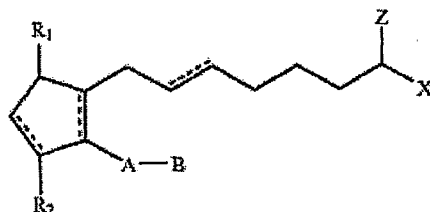
wherein the cosmetic composition includes one or more of a stabilizer and an aqueous vehicle, which compositions are useful in a method for the enhancement of the appearance one or more hair properties such as luster, sheen, brilliance, gloss, glow, shine, patina, length, thickness, density, and/or overall appearance.

[019] Consequently, in certain aspects, the present disclosure is directed to topical compositions that include at least one prostaglandin based compound and/or a derivative and/or analog thereof, which compound may, in certain instances, be formulated in conjunction with a stabilizer. In certain aspects, a topical composition of the disclosure is provided for the conditioning and/or enhancing the look of the skin and/or hair, for instance, the skin comprising the hair of the eyelashes, eyebrows, and scalp, e.g., of a mammal, such as a human. Accordingly, a composition including a prostaglandin based compound of the disclosure will be set out first, followed by the description of the use of such a composition in a cosmetic formulation for increasing the appearance of one or more hair properties, such as luster, sheen, brilliance, gloss, glow, shine, patina, length, thickness, density, and/or overall appearance.

[020] In one aspect, the disclosure provides a composition containing a prostaglandin based compound, which composition may be used for increasing the appearance of one or more hair properties such as luster, sheen, brilliance, gloss, glow, shine, patina, length, thickness, density, and/or overall appearance. Specifically, a prostaglandin based compound of the disclosure may include a prostaglandin, prostamide, derivative, and/or analog thereof, and may optionally include a stabilizing agent. The composition may additionally include a solubilizer, an uptake and/or distribution booster, a thickening agent, a conditioning agent, a moisturizing agent, an anti-oxidant, a surfactant, and/or the like. Hence, in some embodiments, the active ingredients, e.g., a prostaglandin, prostamide, derivative, and/or analog thereof, may be provided as a pre-blend in which a prostaglandin based compound is mixed first with a solubilizer, such as a C<sub>12-15</sub> alkyl benzoate. Any suitable solvent may also be used, e.g., lower alcohols such as isopropanol and/or propylene glycol. Further, a stabilizing agent may also be included. In certain embodiments, a stabilizing agent may be a cyclodextrin, e.g., 2-hydroxypropyl-alpha (or beta)-cyclodextrin, sulfobutyl ether-beta-cyclodextrin, and 2,6-dimethyl-beta cyclodextrin.

[021] The compositions may further include a cosmetically acceptable vehicle, such as a vehicle that acts as a dilutant, dispersant, and/or carrier for the prostaglandin based compound, so as to facilitate its distribution and uptake when the composition is applied to the skin, hair, and/or scalp. The cosmetically acceptable vehicle may vary from, for instance, about 2%-5% to about 99.9%, for instance, from about 25% to about 80%, including about 35% to about 60% by weight of the composition, and can, in the absence of other cosmetic adjuncts, form the balance of the composition.

[022] A prostaglandin, prostamide, derivative, and/or analog thereof in the composition of the disclosure includes a prostaglandin based compound with the following formula:



wherein the dashed bonds represent a single or double bond which can be in the cis or trans configuration,

[023] A is an alkylene or alkenylene radical having from two to six carbon atoms, which radical may be interrupted by one or more oxa radicals and substituted with one or more hydroxy, oxo, alkyloxy or alkylcarboxy groups wherein said alkyl radical comprises from one to six carbon atoms;

[024] B is a cycloalkyl radical having from three to seven carbon atoms, or an aryl radical, selected from the group consisting of hydrocarbyl aryl and heteroaryl radicals having from four to ten carbon atoms wherein the heteroatom is selected from the group consisting of nitrogen, oxygen and sulfur atoms;

X is either  $-N(H)CH(CH_2OH)_2$  or  $-OCH(CH_2OH)_2$ ;

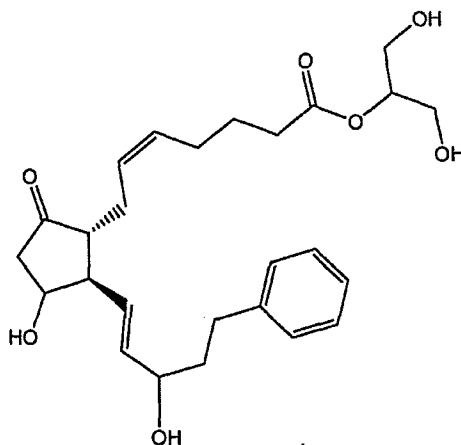
Z is  $=O$ ;

one of  $R_1$  and  $R_2$  is  $=O$ ,  $-OH$  or a  $-O(CO)R_3$  group, and the other one is  $-OH$  or  $-O(CO)R_3$ , or  $R_1$  is  $=O$  and  $R_2$  is  $H$ , wherein  $R_3$  is a saturated or unsaturated acyclic hydrocarbon group having from 1 to about 20 carbon atoms, or  $-(CH_2)_mR_4$  wherein  $m$

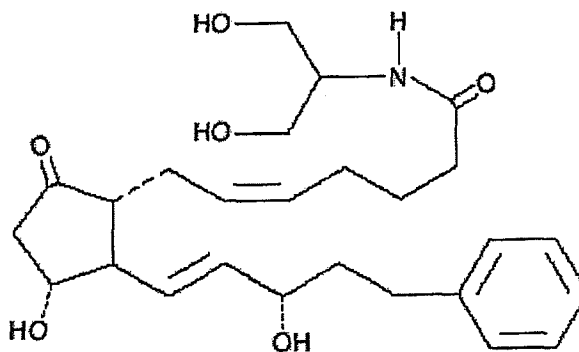


is 0 or an integer of from 1 to 10, and  $R_4$  is cycloalkyl radical, having from three to seven carbon atoms, or a hydrocarbyl aryl or heteroaryl radical, as defined above or a pharmacologically acceptable acid addition salt thereof.

[025] In certain embodiments, the prostaglandin based compound is a prostaglandin or a derivative or analog thereof, such as [(2-hydroxy-1-hydroxymethyl)ethyl]-9-oxo-11,15-dihydroxy-17-phenyl-18, 19, 20-trinor-prosta-5Z, 13E-dien-1-oate. For instance, in certain embodiments, the prostaglandin based compound of the disclosure comprises the following structure:



[026] In certain embodiments, the prostaglandin based compound is a prostamide or a derivative or analog thereof, such as 17-phenyl trinor prostaglandin E2 serinol amide. For instance, in certain embodiments, the prostaglandin based compound of the disclosure comprises the following structure:



[027] As set forth above, the present inventors have postulated that the representative prostaglandin based compounds of the present disclosure are more stable in aqueous environments, and in instances wherein the prostaglandin based compounds are combined with a stabilizer, such as cyclodextrin, are more suited for forming inclusion products therewith than other such compounds heretofore known and used in cosmetic formulations. For instance, without being held to theory, the present inventors have postulated that given the long, strung out structure of the prostaglandin like compounds of the disclosure, and in particular given the chemical nature of the X group, e.g., the  $-N(H)CH(CH_2OH)_2$ , the Applicants believe that a compound of the disclosure is capable of folding back on itself and forming an intermolecular bond with one or more of the  $R_1$  and  $R_2$  of the pentimer ring. For example, it is believed that in solution the diol of the X group may form an intermolecular bond (either through deprotonation and/or hydrogen bonding) with the oxygen containing groups of the pentimer ring, thereby causing the molecule to fold over on itself. It is believed that as a result of this "folding over" the pentimer ring will be better protected from hydrolitic cleavage, and therefore, will be more stable in aqueous solutions, and thus less likely to decompose. Additionally, it is further believed that this "folding over" will allow the molecule to more readily fit within the ring structure of a stabilizing agent such as cyclodextrin.

[028] Specifically, without wishing to be bound by theory, it is postulated that combining a prostaglandin based compound of the disclosure, such as 17-phenyl trinor prostaglandin E2 serinol amide, with a stabilizing agent, such as cyclodextrin, increases the stability and effectiveness of the prostaglandin composition. For instance, as indicated above, cyclodextrin has a toroid or ring-like structure that allows various portions of the prostaglandin based compound of the disclosure to be fit within the cavity of the ring structure so as to form a protective shell around the prostaglandin based compound, which protective shell may protect the pentimer ring from decomposer due to hydrolysis while in solution. For example, because the compound is both folded over and fitted within the cyclodextrin ring, water molecules in the solution will have less access to the reactive  $R_1$  and  $R_2$  groups of the pentimer ring, which consequently may result in less hydrolysis and therefore greater stability in solution.

[029] The cyclodextrin thus may serve at least three main functions, 1) it promotes the solubility of the prostaglandin based compound and thus allows for a greater concentration of the compound to be present in the solution, 2) it protects various reactive groups on the prostaglandin based compound from hydrolysis, thus preventing degradation, and 3) it helps with penetration.

[030] For example, cyclodextrins form toroid structures, which structures include an outer-surface and an inner-surface, wherein the inner surface defines a cavity. Because of the configuration of the toroid structure, the outer surface thereof is comprised of primary and secondary hydroxyl groups, which makes the outer surface relatively hydrophilic. While the outer surface is comprised of hydroxyl groups, the inner surface remains relatively less hydrophilic, and thus, capable of receiving a portion of the hydrophobic prostaglandin based compound of the disclosure within the cavity of the cyclodextrin, which cavity is less hydrophilic than the aqueous environment of the composition. Accordingly, with respect to promoting the solubility of the prostaglandin based compound, without being held to theory, it is postulated that the cyclodextrin molecules suitable for use as stabilizing agents in accordance with the disclosure are capable of forming inclusion products with the prostaglandin based compounds disclosed herein, thereby modifying the compound's typical physical and chemical properties, thus, rendering the naturally hydrophobic prostaglandin based compounds more soluble in aqueous environments.

[031] Further, with respect to the protection of various reactive groups on the prostaglandin based compound from hydrolysis, without being held to theory, it is postulated that the cyclodextrin molecules suitable for use as stabilizing agents in accordance with the disclosure are capable of receiving at least a portion of the cyclopentene ring of the prostaglandin based compounds described herein within the cavity of the toroid structure of the cyclodextrin, thereby protecting any associated =OH and or -OH groups positioned thereon, e.g., at C<sub>9</sub> or C<sub>11</sub>, from hydrolysis. For instance, it is postulated that, as described in greater detail above, the prostaglandin based compounds of the disclosure will be capable of forming intramolecular bonds between the terminal isopropyl diol group and one or more of the -OH groups positioned on the cyclopentene ring, e.g., at C<sub>11</sub>. This folded structure may then be

inserted into the cavity of the cyclodextrin and thereby be protected from degradation due to dehydration.

[032] Additionally, with respect to promoting penetration, without being held to theory, it is postulated that the cyclodextrin molecules suitable for use as stabilizing agents in accordance with the disclosure are capable of acting as a permeation enhancer, for instance, by decreasing the barrier function of lipophilic membranes, such as the lipophilic membrane of the skin. Topical administration of prostaglandin based compounds is problematic because of the barrier to penetration that the stratum corneum, e.g., skin, presents. The skin is comprised of layers, which layers secrete a slightly acidic oily film which functions as a permeation barrier to water and other hydrophilic compositions. Specifically, the skin of the face has a high buffer capacity that actively resists changes in pH.

[033] Accordingly, in order to be effective, a prostaglandin based compound contained within a cosmetic composition of the disclosure must be able to penetrate through the outer, or epidermis, layers of the skin and into the deeper layers of the dermis without greatly affecting the overall pH of the skin. Cyclodextrin helps facilitate the penetration of the prostaglandin based compound in part because it reduces the effect of the composition on the pH barrier of the skin. Hence, a prostaglandin based compound, when complexed with cyclodextrin, or other stabilizing agent, is able to form a synergistic combination that promotes the penetration of the prostaglandin based compound through the epidermis and into the dermal regions of the skin without substantially disrupting the pH barrier of the skin. Specifically, without being held to theory, it is postulated that the cyclodextrin forms an inclusion complex with the prostaglandin based compound, wherein the cyclodextrin acts as permeation enhancer carrying the prostaglandin based compound through the aqueous barrier of the cosmetic solution, from the bulk solution towards the lipophilic surface of epidermis and into the dermis, wherein the prostaglandin based compound partitions from the complex and into the dermis.

[034] Any suitable cyclic oligosaccharide may be used as a stabilizing agent in combination with a prostaglandin based compound of the disclosure. A suitable cyclic oligosaccharide may be an oligosaccharide composed of 5 or more  $\alpha$ -D-glucopyranosides. For instance, in certain embodiments, the cyclic oligosaccharide

may be a cyclodextrin, such as an  $\alpha$ -,  $\beta$ - (e.g., Cavamax W7®),  $\gamma$ -cyclodextrin, or the like. For example, the cyclodextrin may be a 2-hydroxypropyl-alpha-cyclodextrin, 2-hydroxypropyl-beta-cyclodextrin, sulfobutyl ether-beta-cyclodextrin, 2,6-dimethyl-beta cyclodextrin, or other alkylcyclodextrin, such as methylcyclodextrin, and the like. Other suitable agents capable of forming complexes with the prostaglandin based compounds of the disclosure may also be used as a stabilizing agent. For instance, a suitable stabilizing agent may include dextran, dextrin, pullulan, derivatives and/or analogs thereof.

[035] Accordingly, in one aspect, a composition of the disclosure includes one or more of a prostaglandin based compound and/or an derivative and/or analog thereof in a synergistic combination with one or more stabilizers (as described above), solubilizers, buffering agents, cosmetically acceptable vehicles, and the like. For instance, in various embodiments, a suitable buffering agent may be NaOH, Ammonia, Citric Acid, KOH, Benzoic Acid, TEA, AMP, or the like. Specifically, the prostaglandin based active ingredients may be provided as a pre-blend in which a prostaglandin based compound of the disclosure is mixed with a solublizer, such as a C<sub>12-15</sub> alkyl benzoate, or may be provided as a direct blend, e.g., not provided prior in a pre-blend such as with C<sub>12-15</sub> alkyl benzoate. A suitable solvent may also be included, e.g., a lower alcohol, such as isopropanol and/or propylene glycol.

[036] The cosmetic composition may also include a cosmetically acceptable vehicle, which vehicle may act as a dilutant, dispersant, or carrier for the prostaglandin based compound, so as to facilitate its distribution and uptake when the composition is applied to the skin, hair, and/or scalp. The cosmetically acceptable vehicle may function, in part, to facilitate the distribution and uptake of the prostaglandin based compound when the composition is applied to the skin and/or hair or scalp. Cosmetically acceptable vehicles may include water, and/or other liquid or solid emollients, solvents, humectants, thickeners and powders.

[037] A cosmetically acceptable vehicle may comprise from about 2%-5% or less to about 99.9% or more, such as from about 25% to about 80%, including about 40% to about 60% by weight of the composition. Vehicles other than or in addition to water can include liquid or solid emollients, solvents, humectants, thickeners and powders. The cosmetic composition may comprise an aqueous, aqueous/alcoholic or oily

solution; dispersion of the lotion type; anhydrous or lipophilic gel; emulsions of liquid or semi-liquid consistency, which may be obtained by dispersion of a fatty phase in an aqueous phase (O/W) or conversely (W/O); or may comprise a suspension or emulsion of smooth, semi-solid or solid consistency of the cream or gel type.

[038] Accordingly, a cosmetic composition of the disclosure may be formulated as a lotion, which lotion may be prepared so as to be applied to the skin, and may comprise a liquid or semiliquid preparation in which solid particles, including the prostaglandin based compound of the disclosure, are present in a lipid, alcohol or water base. A suitable lotion of the disclosure may be a suspension of solids, and may include a liquid oily emulsion of the oil-in-water type. A suitable lotion may also include a suspending agent, so as to produce a better dispersion, as well as a compound useful for localizing and holding the prostaglandin based compound in contact with the skin, e.g., methylcellulose, sodium carboxymethyl-cellulose, or the like.

[039] A suitable solution may comprise a homogeneous mixture prepared by dissolving one or more chemical substances (solute) in another liquid such that the molecules of the dissolved substance may be dispersed among those of the solvent. The solution may contain other cosmetically acceptable chemicals to buffer, stabilize or preserve the solute as described herein. Suitable solvents may include ethanol, water, propylene glycol or any other cosmetically acceptable vehicle known in the art.

[040] When a composition of the disclosure is formulated as an oily solution or gel, the fatty phase may constitute more than 90% of the total weight of the composition. When the composition is formulated as an emulsion, the proportion of the fatty phase may range from about 5% to about 80% by weight, and may range from about 10% to about 50% by weight, relative to the total weight of the composition. Oils, emulsifiers and co-emulsifiers incorporated in the composition in emulsion form may be selected from among those known in the art. The emulsifier and coemulsifier may be present in the composition at a proportion ranging from about 0.03%-3% or less to about 30% or more by weight, for instance, from about 0.5% to about 20% by weight, relative to the total weight of the composition.

[041] Suitable oils that may be used include mineral oils (liquid petrolatum), plant oils (liquid fraction of karite butter, sunflower oil), animal oils (perhydrosequalen(e),

synthetic oils (purcellin oil), silicone oils (cyclomethicone) and fluoro oils (perfluoropolyethers). Fatty alcohols, fatty acids (stearic acid) and waxes (paraffin wax, carnauba wax and beeswax) may also be used as fats. Emulsifiers that may be used include glyceryl stearate, polysorbate 60, PEG-6/PEG-32/glycol stearate mixture, *etc.* Solvents that may be used include the lower alcohols, such as ethanol, isopropanol, and propylene glycol.

- [042] An oil or oily material may be present, together with an emollient to provide either a water-in-oil emulsion or an oil-in-water emulsion, depending largely on the average hydrophilic-lipophilic balance (HLB) of the emollient employed. Levels of such emollients may range from about 0.5% to about 50%, preferably between about 5% and 30% by weight of the total composition. Emollients may be classified under such general chemical categories as esters, fatty acids and alcohols, polyols and hydrocarbons.
- [043] Esters may be mono- or di-esters. Acceptable examples of fatty di-esters include dibutyl adipate, diethyl sebacate, diisopropyl dimerate, and dioctyl succinate. Suitable straight chain fatty esters include lauryl palmitate, myristyl lactate, oleyl eurate and stearyl oleate. Preferred esters include coco-caprylate/caprate (a blend of coco-caprylate and coco-caprate), propylene glycol myristyl ether acetate, diisopropyl adipate and cetyl octanoate. Suitable branched chain fatty esters include 2-ethyl-hexyl myristate, isopropyl stearate and isostearyl palmitate. Suitable tribasic acid esters include triisopropyl trilinoleate and trilauryl citrate.
- [044] Suitable fatty alcohols and acids include those compounds having from 10 to 20 carbon atoms, such as cetyl, myristyl, palmitic and stearyl alcohols and acids. Among the polyols which may serve as emollients are linear and branched chain alkyl polyhydroxyl compounds. For example, propylene glycol, sorbitol and glycerin are preferred. Polymeric polyols, such as polypropylene glycol and polyethylene glycol, may also be used. Butylene and propylene glycol may be used as penetration enhancers.
- [045] Exemplary hydrocarbons which may serve as emollients are those having hydrocarbon chains anywhere from 12 to 30 carbon atoms, such as, mineral oil, petroleum jelly, squalene and isoparaffins.

- [046] The compositions of the invention may contain a surfactant in an aqueous base. The surfactants can be present, alone or in a mixture, and may be contained in an amount from about 1 to about 50 % by weight, for instance, from about 2.5 to about 30 % by weight, including about 2-5% to about 20% by weight. Nonionic surfactants, amphoteric surfactants, zwitterionic surfactants and anionic surfactants may also be used.
- [047] Suitable anionic surfactants include, e.g. alkaline or alkaline earth salts, alpha-olefin sulfonates, sulfosuccinates, disodium laureth-3 sulfosuccinate, disodium PEG-5 lauryl citrate sulfosuccinate, disodium ricinolamido MEA-sulfosuccinate or disodium laurylamido MEA-sulfosuccinate and alkyl ether carboxylates.
- [048] Suitable nonionic surfactants include e.g. alkoxyated fatty alcohols, alkoxyated fatty acid esters, alkoxyated partial glycerides, saturated or unsaturated fatty acids, alkoxyated polyol esters, and alkylpolyglucosides, such as coconut glucosides, lauryl glycosides or decylglucosides. For example, ethoxylated lauryl alcohol, tetradecyl alcohol, cetyl alcohol, oleyl alcohol or stearyl alcohol, which are used alone or in mixtures with each other, as well as fatty alcohols of ethoxylated lanolin, are suitable as fatty alcohol ethoxylates. Furthermore the ethoxylated fatty acid sugar esters known as nonionic surfactants, especially ethoxylated sorbitan fatty acid ester, are suitable for use in the cosmetic preparations according to the invention. The suitable ethoxylated fatty acid sugar esters include those marketed under the trade names Tween™ and Arlacel™ by ICI surfactants and the alkyl-polyglycosides, which are marketed under the trade names Plantaren™ or Plantacare™ by Henkel or under the trade name Oramix™ by Seppic.
- [049] Suitable hydrophobic (water-insoluble) surfactants, include, for example, an emulsifying wax, polyoxyethylene acid, polyoxyethylene alcohol, glycerol monostearate, sorbitan tristearate, sorbitan monopalmitate, sorbitan sesquileate, and other sorbitan fatty acid ester. Anionic surfactants, nonionic surfactants, amphoteric surfactants, and zwitterionic surfactants may also be used. For instance, suitable anionic surfactants include, e.g. alkaline or alkaline earth salts, alpha-olefin sulfonates, sulfosuccinates, disodium laureth-3 sulfosuccinate, disodium PEG-5 lauryl citrate sulfosuccinate, disodium ricinolamido MEA-sulfosuccinate or disodium laurylamido MEA-sulfosuccinate and alkyl ether carboxylates. Suitable nonionic surfactants may



include *e.g.* alkoxylated fatty alcohols, alkoxylated fatty acid esters, alkoxylated partial glycerides, saturated or unsaturated fatty acids, alkoxylated polyol esters, and alkylpolyglucosides, such as coconut glucosides, lauryl glycosides or decylglucosides. For example, ethoxylated lauryl alcohol, tetradecyl alcohol, cetyl alcohol, oleyl alcohol or stearyl alcohol, which are used alone or in mixtures with each other, as well as fatty alcohols of ethoxylated lanolin, are suitable as fatty alcohol ethoxylates. Furthermore the ethoxylated fatty acid sugar esters known as nonionic surfactants, especially ethoxylated sorbitan fatty acid ester, are suitable for use in the cosmetic preparations according to the invention. The suitable ethoxylated fatty acid sugar esters include those marketed under the trade names Tween™ and Arlacel™ by ICI surfactants and the alkyl-polyglycosides, which are marketed under the trade names Plantaren™ or Plantacare™ by Henkel or under the trade name Oramix™ by Seppic. Suitable amphoteric surfactants may include for example betaines, such as cocoamidopropylbetaine or lauryl betaine, sulfobetaines, such as cocoamidopropyl hydroxysultaine, glycinate, such as cocoamphoglycinate (INCI-name: sodium cocoamphoacetate) and diglycinates and propionates, such as cocoampho-propionate. A surfactant may be present, alone or in a mixture, and may be contained in an amount that ranges from about 1 % or less to about 50 % or more by weight, especially preferably from 1 to 30 % by weight.

[050] The compositions of the disclosure may also include additives and adjuvants, such as hydrophilic or lipophilic gelling agents, hydrophilic or lipophilic active agents, preservatives, antioxidants, solvents, fragrances, fillers, bactericides, odor absorbers and dyestuffs or colorants. The amounts of these various additives and adjuvants may range from about 0.01% or less to 10% or more of the total weight of the composition. Depending on their nature, these additives and adjuvants may be introduced into the fatty phase or into the aqueous phase.

[051] A suitable thickener may also be included. A thickener may be present in an amount that ranges from about 0.01% or less to about 20% or more by weight, such as from about 0.5%-1% to 10% by weight of the composition. Suitable thickeners may be cross-linked polyacrylate materials, such as Carbopol. Gums may also be employed, such as xanthan, carrageenan, gelatin, karaya, pectin, locust beans gum, and the like. The thickening function may also be accomplished by a material that also serves as a

silicone or emollient. For instance, silicone gums in excess of 10 centistokes and esters such as glycerol stearate, which have dual functionality, may be included. Suitable gelling agents may include a hydrophilic gelling agent. Hydrophilic gelling agents include carboxyvinyl polymers (carbomer), acrylic copolymers such as acrylate/alkylacrylate copolymers, polyacrylamides, polysaccharides, such as hydroxypropylcellulose, natural gums and clays, and, as lipophilic gelling agents, representative are the modified clays such as bentones, fatty acid metal salts such as aluminum stearates and hydrophobic silica, or ethylcellulose and polyethylene.

[052] The cosmetic composition of the disclosure may also include a suitable powder. Suitable powders include chalk, talc, kaolin, starch, smectite clays, chemically modified magnesium aluminum silicate, organically modified montmorillonite clay, hydrated aluminum silicate, fumed silica, aluminum starch octenyl succinate and mixtures thereof.

[053] Other adjunct components may also be incorporated into the cosmetic compositions. Such ingredients may include coloring agents, opacifiers and perfumes. Specifically, these ingredients may include cosmetically suitable additives such as deionized water, hydrolyzed glycosaminoglycan, sodium hyaluronate, triethanolamine, propylene glycol, methylparaben, propylparaben, acrylates, C10-C20 alkyl acrylate crosspolymers, C12-C15 alkyl benzoate, panthenol, biotin, sodium chloride, sodium phosphate and the like. Amounts of such other adjunct components may range from about 0.001% or less up to about 20% or more by weight of the composition.

[054] In certain aspects, a prostaglandin based composition of the disclosure may be a hair conditioning composition, such as rinse-out hair care composition (e.g., rinses, treatments) and/or a leave-on hair product. Such hair care compositions may be based on O/W emulsions and contain water, and at least one hydrophobic ingredient (especially at least one fatty alcohol).

[055] The amount and concentration of the prostaglandin based compound in the compositions of the disclosure may vary on several factors, such as: the pH and condition of the skin, oil content, and the interaction between the various constituents included in the composition, but should be such to be effective to at least enhance the

appearance of one or more properties associated with hair follicles in a subject, such as luster, sheen, brilliance, gloss, glow, shine, patina, length, thickness, density, overall appearance of the hair, and/or the like. For instance, a cosmetic composition may include at least about 0.00001%, such as at least about .0001%, for instance, at least about 0.001%, for example, at least about 0.01%, at least about 0.03%, at least about 0.1%, at least about .2%, at least about .3%, at least about 3.5%, at least about 1%, at least about 2.5%, at least about 5% or more, and usually not more than about 10% - 20% or about 30% - 50% (weight/weight) of a prostaglandin based compound as an active ingredient. The cosmetically acceptable vehicle, on the other hand, may form from about 2%-5% or less to about 99.9% or more, for instance, from about 25% to about 80%, including about 35% to about 60% by weight of the composition, and can, in the absence of other cosmetic adjuncts, form the balance of the composition.

[056] In certain embodiments, a composition of the disclosure is formulated as a topical composition that releases the prostaglandin based compound all at once upon application, so as to produce a highly concentrated layer of the prostaglandin based compound on the surface of the skin, which therefore may work on the outer layer of the skin before absorption thereby. However, in certain embodiments, a composition of the disclosure may be formulated in conjunction with a controlled release mechanism, such as a microsphere, liposome, microcapsule, polymer, gel, hydrophilic gum, and/or other colloidal drug delivery systems, so as to produce a prolonged release effect which may reduce or prevent excessive accumulation of the prostaglandin based compound within the epidermis and the dermis, so as to allow for greater penetration of the prostaglandin based compound. Because of the sustained release, the use of such controlled release mechanisms, in conjunction with the cosmetic carrier, can significantly reduce the irritation of the prostaglandin based compound without reducing its efficacy.

[057] Accordingly, in certain embodiments, the composition may be provided in a substance or carrier that facilitates penetration and/or includes a controlled release mechanism. Examples of controlled release mechanisms include microspheres, microspheres, liposomes, microcapsules, polymers, gels, hydrophilic gums, and/or other colloidal drug delivery systems. Hence, a cosmetic composition of the disclosure

may include one or more of: microsponges, microspheres (e.g., micelles), and/or liposomes.

[058] For instance, the composition may include a controlled release mechanism such as a microsphere. Microspheres are microscopic, porous spherical sponges. Generally, microspheres are porous microspheres having a myriad of interconnected voids of particle size range 5-300 $\mu$ m. Depending upon the size, the total pore length may range up to 10 ft and pore volume may range up to 1 ml/g. A suitable microsphere of the disclosure has the capacity to entrap a prostaglandin based compound and/or other cosmetically suitable compound, such as an emollient, surfactant, essential oils, sunscreen and anti-infective, etc. and can be used with the prostaglandin based compound of the disclosure as a topical carrier system. The prostaglandin based compound of the disclosure can be incorporated in to a microsphere and formulated into creams, lotions and powders. Other forms of microspheres may be incorporated into the present formulations of the disclosure, such as those formed from lipids, typically charged lipids, such as phospholipids.

[059] Further, the composition may include a controlled release mechanism such as a microsphere or micelle. Micelles are comprised of surfactant molecules that are arranged so that their polar headgroups form an outer spherical shell, while the hydrophobic, hydrocarbon chains are oriented towards the center of the sphere, forming a core. Micelles form in an aqueous solution containing surfactant at a high enough concentration so that micelles naturally result. Surfactants useful for forming micelles may include, potassium laurate, sodium octane sulfonate, sodium decane sulfonate, sodium dodecane sulfonate, sodium lauryl sulfate, docusate sodium, decyltrimethylammonium bromide, dodecyltrimethylammonium bromide, tetradecyltrimethylammonium bromide, tetradecyltrimethyl-ammonium chloride, dodecylammonium chloride, polyoxyl 8 dodecyl ether, polyoxyl 12 dodecyl ether, nonoxynol 10 and nonoxynol 30.

[060] Additionally, the composition may include a controlled release mechanism such as a liposome. Liposomes are vesicles having a lipid wall comprising a lipid bilayer. Liposomal preparations for use in the instant disclosure include cationic (positively charged), anionic (negatively charged) and neutral preparations. Cationic liposomes are readily available. For example, N-[1-2,3-dioleoyloxy)propyl]-N,N,N-triethylammonium

liposomes are commercially available. Anionic and neutral liposomes are commercially and readily available as well, or can be easily prepared using readily available materials. Such materials may include phosphatidyl choline, cholesterol, phosphatidyl ethanolamine, dioleoylphosphatidyl choline, dioleoylphosphatidyl glycerol, dioleoylphosphatidyl ethanolamine, among others. These materials may be mixed with N-[1-2,3-dioleoyloxy)propyl]-N,N,N-triethylammonium (DOTMA) in appropriate ratios. Methods for making liposomes using these materials are well known in the art.

[061] The cosmetic compositions of the present disclosure may also contain agents that sooth or condition the skin and hair ("conditioning agents"). One such agent is panthenol, a pro-vitamin moisturizing agent, such as Vitamin E. Panthenol is may be incorporated into the cosmetic formulations of the disclosure and may promote the penetration of the prostaglandin based compound into the skin and hair. Panthenol derivatives (e.g., ethyl panthenol) also find use in the compositions of the disclsoure as do agents such as aloe vera, pantothenic acid and its derivatives, allantoin, bisabolol, and dipotassium glycyrrhizinate. For instance, a hair conditioning agent may be a hydrolyzed wheat protein, which may be included so as to improve the hair's resilience and promote body by penetrating the hair shaft to repair damage and is provided in an amount from about 5 to 25% by weight.

[062] Other hair and skin conditioning/soothing agents may also be included in the subject compositions. For example, one or more anti-microbial agents can be included in the composition, e.g., leuconostoc/radish root ferment filtrate. If desired, a pH stabilizer such as triethanolamine can be included in the composition, as can anti-oxidants, such as ascorbyl palmitate, tocopheryl acetate, L-carnosine, Carotenoids, Co-Enzyme Q10, Vitamin A, B, C, D, and/or E, Green Tea extract, Selenium, Zinc, and the like; or a moisturizing agent such as xodium hyaluronate; or a chelator, such as ethylenediamine, porphine, EDTA (ethylenediamine tetraacetate), DMSO, DMSO<sub>2</sub> (MSM), sodium phytate, DTPA (Diethylenetriaminepentaacetic acid), NTA ACID (Nitrilotriacetic acid), and the like..

[063] Other minor components may also be incorporated into the cosmetic compositions. These ingredients may include coloring agents, opacifiers and perfumes.

Amounts of these other minor components may range anywhere from about 0.001% or less up to about 20% or more by weight of the composition.

Preparing Compositions of the Invention

[064] In certain embodiments, in preparing a composition of the disclosure, a prostaglandin derivative described above may be mixed with a dermatologically compatible vehicle or carrier. The vehicle may comprise, for example, aqueous solutions, such as e.g., physiological salines, oil solutions, and/or ointments. The vehicle furthermore may contain dermatologically compatible preservatives, such as e.g., benzalkonium chloride; surfactants like e.g., polysorbate 80; liposomes or polymers, for example, methyl cellulose, polyvinyl alcohol, polyvinyl pyrrolidone and hyaluronic acid; and/or other agents that may be used for increasing the viscosity. Furthermore, it is also possible to use soluble or insoluble drug inserts when the drug is to be administered.

[065] Effective amounts of the prostaglandin based compound will vary depending on the compound employed, frequency of application and desired result, but will generally range from about 0.0000001 to about 50% by weight of the dermatological composition. Representative compositions may thus comprise from about 0.001 to about 50 $\mu$ g of the derivatives in about 1 to about 100 $\mu$ g of total dermatological composition, more preferably from about 0.1 to about 30  $\mu$ g in about 10 to about 50 $\mu$ g of the composition. Depending on the actual formulation and prostaglandin based compound to be used, various amounts of the drug and different dose regimens may be employed for delivery.

[066] Accordingly, in certain aspects, a composition of the disclosure may be delivered or otherwise administered to a subject for the enhancement of the appearance of one or more properties associated with hair follicles in a subject, such as luster, sheen, brilliance, gloss, glow, shine, patina, length, thickness, density, or overall appearance of the hair. As described above the composition may be a prostaglandin based compound, such as a prostaglandin, prostamide, and/or a derivative or analog thereof, and may be delivered by itself or in association with a stabilizing agent, and/or with a topical cosmetic carrier. The method may include the provision of a suitably formulated composition of the disclosure and the contacting of the composition with the skin of the user. The contacting may be performed via the use of a contacting

facilitator such as a brush or swab or other applicator, and the contacting may be performed by brushing, dabbing, rubbing, and/or using any other manner known in the art for contacting a composition of the disclosure with the skin and/or hair of the user.

[067] For instance, the skin to be contacted may be the skin surrounding the eyelids, eyebrows, and/or the head of the user. In some instances, the skin to be contacted is skin that is associated with hair follicles. Accordingly, in certain embodiments, such as where the composition is formulated as an aqueous solution, an effective amount of a composition of the disclosure may be applied to the skin and/or hair by contacting a suitable applicator to the composition to be administered, so as to wet the applicator, and subsequently contacting the skin of the user with the wetted applicator. In other embodiments, such as where the composition is formulated as a topical cream, lotion, ointment, wash, rinse, or conditioner, an effective amount of the composition may be applied to the hands, a towel, swab, and/or the like, and then applied to the skin and/or hair to be contacted by rubbing. Additionally, where the composition comprises a powder, the powder may be applied by patting and/or dabbing; and where the composition is formulated as an aerosol, the contacting may be effectuated by spraying the area to be contacted with the appropriately formulated aerosol composition.

[068] The present disclosure finds application in all mammalian species, including both humans and animals. In humans, the compounds of the subject disclosure can be applied for example, to the scalp, face, beard, head, pubic area, upper lip, eyebrows, and eyelids. In animals raised for their pelts, e.g., mink, the compounds can be applied over the entire surface of the body to improve the overall pelt for commercial reasons. The process can also be used for cosmetic reasons in animals, e.g., applied to the skin of dogs and cats having bald patches due to mange or other diseases causing a degree of alopecia.

[069] The cosmetic compositions of the invention include cosmetic compositions suited for topical and local action. The term "topical" as used herein relates to the use of a prostaglandin based compound, derivative or analogue as described herein, incorporated in a suitable cosmetic carrier, and applied at the site for exerting local action. Accordingly, such topical compositions including those forms in which the compound is applied externally by direct contact with the skin surface to be treated. Conventional cosmetic forms for this purpose include ointments, liniments, creams,

shampoos, lotions, pastes, jellies, sprays, aerosols, and the like, and may be applied in patches or impregnated dressings depending on the part of the body to be treated. The term "ointment" embraces formulations (including creams) having oleaginous, absorption, water-soluble and emulsion-type bases, e.g., petrolatum, lanolin, polyethylene glycols, as well as mixtures of these.

[070] For topical use on the eyelids or eyebrows, the active prostaglandin based compounds, as well as their derivatives and analogues, including esters and salts, can be formulated in aqueous solutions, creams, ointments or oils exhibiting physiologically acceptable osmolarity by addition of pharmacologically acceptable buffers and salts, as described herein above. Such formulations may or may not, depending on the dispenser, contain preservatives, such as benzalkonium chloride, chlorhexidine, chlorobutanol, parahydroxybenzoic acids and phenylmercuric salts such as nitrate, chloride, acetate, and borate, or antioxidants, as well as additives like EDTA, sorbitol, boric acid etc. as additives. Furthermore, particularly aqueous solutions may contain viscosity increasing agents such as polysaccharides, e.g., methylcellulose, mucopolysaccharides, e.g., hyaluronic acid and chondroitin sulfate, or polyalcohol, e.g., polyvinylalcohol. Various slow releasing gels and matrices may also be employed as well as soluble and insoluble ocular inserts, for instance, based on substances forming in-situ gels.

[071] Depending on the actual formulation and prostaglandin based compound to be used, various amounts of the compound and different dose regimens may be employed. In use, a quantity of the composition, for example from about 0.0001 ml to about 100 ml, from about 0.001 ml to about 10 ml, from about 0.01 ml to about 1 ml, such as from about 0.1 ml is applied to a site of interest (i.e., skin or hair of the eyelash, eyebrow, and/or scalp) from a suitable container or applicator and, if necessary, it may then spread over and/or rubbed into the site using a suitable device or the hand or finger. For instance, the daily amount of the prostaglandin based compound for contact with the eyelid may be about 0.1 ng to about 100 mg per eyelid, more preferably about 1 ng to about 100 µg per eyelid. For example, in some embodiments, a topical application of a composition of the disclosure may involve the application of a dosage of about 1.5 µg/ml per area to be contacted, e.g., eyelid, per day. However, this application may be increased to twice or three times daily as desired.



[072] The duration of the administration may vary dependent on the desired effects and in certain embodiments should be maintained to ensure the maintenance of said desired effects. For instance, the duration may be for 1, 2, 4, 6, 8, 10, 12, or more weeks or more. For example, the duration may be daily or twice daily for 1, 2, 4, 6, 8, 10, 12 or more months. In some embodiments, a regime may be set up wherein the application occurs once or twice daily for the first month, two, or three, or more, and then a maintenance period begins wherein a once, twice, or three times a week application occurs. In this manner an individual dosage regime may be set up so as to maximize the users desired results.

[073] The product may be specifically formulated for use as a conditioner for a specific area, e.g. the eyelashes, eyebrows, the face, the hair, or the scalp. To achieve the daily amount of conditioning depending on the formulation, the prostaglandin based compound may be administered once or several times daily with or without antioxidants.

[074] In certain aspects, the disclosure is directed to a kit wherein the kit may include: a composition of the disclosure, where the composition is contained within a suitable container, such as a jar, tube, vial, aerosol can, or the like; directions for using the composition; and/or suitable packaging for containing one or more of the composition, container, and/or directions. In certain embodiments, the directions for use may be included on or in the packaging. For instance, in certain embodiments, the directions may be written or printed out on a separate piece of paper, or may be digitally encoded, for instance, on a CD or DVD Rom device. In certain embodiments, the directions for use may simply be a reference to where a more detailed set of instructions for use may be obtained, for instance, an on-line web address.

[075] An exemplary composition of the disclosure will be illustrated in the following non-limiting examples.

[076] Example 1. Pre-blend Composition

%W/W	Ingredients:	INCI:
93.80%	Cetiol AB (Phase A)	C12-15 Alkyl Benzoate

4.20%	Prostaglandin Based Compound (Phase B)	17-phenyl trinor Prostaglandin E2 serinol amide
2.00%	SDA 40B (Phase C)	Ethanol

[077] Pre-blend ingredient list:

[078] The Cetiol AB (including C12-15 alkyl benzoate) may be present in QS.

[079] Prostaglandin E<sub>2</sub> or derivative thereof may be present in an amount that ranges from about 0.001% or less to about 15% or more, such as from about 0.01% to about 12%, including about 0.1% to about 10%, for instance, from about 1% to about 5%, including about 4-4.5%.

[080] The SDA 40B (e.g., Ethanol) may be present in an amount from about 0.001% or less to about 15% or more, such as from about 0.01% to about 10%, including about 0.1% to about 9%, for instance, from about 1% to about 8%.

[081] This blend may then be mixed in the final formulation at about, for example, 0.34%.

[082] Exemplary method for preparing a pre-blend:

1. In a small container, weigh Prostaglandin Based Compound of the disclosure.
2. Add Ethanol.
3. Add C12-15 Alkyl Benzoate and mix for 10 minutes, solution should be clear.
4. Mix and add to eyelash luster enhancing composition.

[083] Example 2. Direct-blend Composition

% W/W	Ingredients:	INCI:
4.20%	Prostaglandin Based Compound (Phase B)	17-phenyl trinor Prostaglandin E2 serinol amide

[084] Direct-blend ingredient list:

[085] In certain embodiments, the Prostaglandin E<sub>2</sub> or derivative thereof may be present in an amount that ranges from about 0.001% or less to about 15% or more, such as from about 0.01% to about 12%, including about 0.1% to about 10%, for instance, from about 1% to about 5%, including about 4-4.5%. This direct-blend may be mixed directly into the final formulation, e.g., without prior blending with C12-15 Alkyl Benzoate and/or ethanol, at about, for example, 0.30%.

[086] Exemplary method for preparing a pre-blend:

1. In a small container, weigh Prostaglandin Based Compound of the disclosure.
2. Add to eyelash luster enhancing composition directly.

[087] Example 3. Eyelash luster enhancing composition

% W/W	Ingredients:	INCI:
85.53%	Water	Water
0.35%	Cavamax	Cyclodextrin
0.60%	Pemulen	Acrylates/C10-30 Alkyl Acrylate Crosspolymer
0.10%	Panthenol	Panthenol
0.03%	Ritaloe 200M	Aloe Barbadensis Leaf Juice
2.00%	AMS Leucidal Liquid	Leuconostoc/Radish Root Ferment Filtrate
0.80%	TEA 99%	Triethanolamine
0.25%	Liposome ACE	Water (and) Phospholipids (and) Retinyl Palmitate (and) Ascorbyl Palmitate (and) Tocopheryl Acetate
10.00%	Actiglide	Water (and) Sodium Hyaluronate (and) Hydrolyzed Glycosaminoglycans
0.3% - 0.34%	Eyelash Pre- or Direct- blend	

[088] Exemplary method for preparing eyelash luster enhancing composition:

1. In a small container add Phase B.
2. Add Phase C.
3. Add Phase A and mix for about 10 minutes, solution should be clear.

Finished formula

A-Water -QS

A-Cavamax -0-5%

A-Pemulen -0-1%

A-Panthenol -0-1%

A-Ritaloe 200M -0-1%

B-AMS Leucidal Liquid -0-2.5%

C-TEA 99% -0-1%

D-Liposome ACE -0-1%

D-Actiglide -0-20%

D-Eyelash Preblend -0-5%

[089] Specifically, charge water into main and begin propeller mixing. Sift in each ingredient of Phase A and mix until completely dispersed. Switch to sweep mixing. Add Phase B. Add Phase C. And Add Phase D.

[090] Final pH of the formulation may be adjusted so to be in a range of about pH-5.0-6.5.

[091] Example 4. Evaluation of Composition:

[092] A prostaglandin based composition of the disclosure, such as that set forth above in Example 3, was studied so as to evaluate the ability of the composition to enhance the appearance of one or more properties associated with hair follicles in a subject, such as luster, sheen, brilliance, gloss, glow, shine, patina, length, thickness, density, or overall appearance of the hair, as well as to evaluate the potential for irritation. Thirty-five female subjects were tested. Each subject was provided with the prostaglandin based composition and given instructions as to its use. Specifically, test subjects were instructed to apply the prostaglandin based composition to the root of the upper lashes of both eyes, following makeup removal, once nightly for twelve weeks.

[093] Computerized consumer perception questionnaires were completed by each subject at the end of Weeks: 2, 4, 6, 8, and 12. A questionnaire setting forth several inquiries with regard to the efficacy of the prostaglandin based composition following use. The questionnaires were designed to provide an efficient and accurate method of determining the test subject's response proportions and to assess the consensus opinion

of the clinical study population. Questionnaire responses were analyzed by Z-tests. The Z-tests were used to determine the statistically significant differences in the proportions of test subjects responding positively or negatively to each test parameter questioned and offering a range of responses. The proportions of subjects choosing the neutral response were split equally and added to the response proportion of the top and bottom choices. The split proportions were compared by the calculation of the Z-Score so as to determine the statistically significant differences. Statistical significance was determined to exist for Z-Scores greater than or equal to the absolute value of 1.96 at the 95% confidence level.

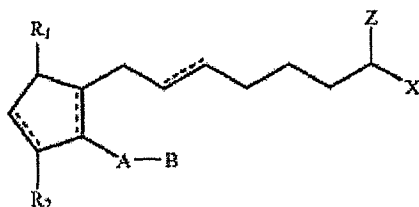
[094] Subjective and objective ocular examinations were performed at Weeks: 0, 6, and 12. Specifically, the ocular status of the test subjects was assessed with regard to several examination parameters including: the degree of lacrimation; redness, scaling, swelling, and meibomian secretions of the eyelids; follicular and/or papillary reaction of the palpebral conjunctivae; evidence of inflammation or abnormalities of the bulbar conjunctivae; evidence of neovascularization, edema, infiltrates, opacities, and/or epithelial defects of the cornea; evidence of scratches and deposits on contact lenses; and intraocular pressure.

[095] Of the 35 subjects tested, 77.1% acknowledged that a prostaglandin based composition of the disclosure enhanced the condition of the lashes after 4 weeks of use. 70.0% acknowledged that the composition made the lashes softer after 2 weeks of use and 80.0% acknowledged this after 6 weeks of use. 67.1% acknowledged that the composition made the lashes feel silkier after 2 weeks of use and 78.6% acknowledged this after 6 weeks of use. 68.6% acknowledged that the composition made the lashes less sparse after 4 weeks of use and 68.6% acknowledged this after 6 weeks of use. 61.4% acknowledged that a prostaglandin based composition of the disclosure enhanced the appearance of the length of the lashes after 4 and 6 weeks of use. 61.4% acknowledged that a prostaglandin based composition of the disclosure enhanced the appearance of the length of the lashes after 4 and 6 weeks of use. 67.1% acknowledged that the composition enhanced the appearance of the thickness of the lashes after 4 weeks of use. 61.4% acknowledged that the composition enhanced the appearance of the fullness of the lashes after 4 and 6 weeks of use. 67.1% acknowledged that the composition made the lashes healthier looking after 4 weeks of use and 68.6%

acknowledged this after 6 weeks of use. 67.1% acknowledged that the composition enhanced the lashes natural look after 4 weeks of use and 74.3% acknowledged this after 6 weeks of use. Additionally, 68.6% acknowledged that the prostaglandin based composition of the disclosure enhanced the overall appearance of the lashes after 4 weeks of use and 70.0% acknowledged this after 6 weeks of use.

What is claimed is:

1. A topical composition for application to mammalian skin, eyebrow or eyelash comprising
  - an effective amount of a prostaglandin based compound; and
  - optionally, a biologically acceptable carrier,
  - wherein said prostaglandin based compound is



wherein the dashed bonds represent a single or double bond which can be in the cis or trans configuration,

A is an alkylene or alkenylene radical having from two to six carbon atoms, which radical may be interrupted by one or more oxa radicals and substituted with one or more hydroxy, oxo, alkyloxy or alkylcarboxy groups wherein said alkyl radical comprises from one to six carbon atoms;

B is a cycloalkyl radical having from three to seven carbon atoms, or an aryl radical, selected from the group consisting of hydrocarbyl aryl and heteroaryl radicals having from four to ten carbon atoms wherein the heteroatom is selected from the group consisting of nitrogen, oxygen and sulfur atoms;

X is either  $-N(H)CH(CH_2OH)_2$  or  $-OCH(CH_2OH)_2$ ;

Z is =O;

one of R<sub>1</sub> and R<sub>2</sub> is =O, -OH or a  $-O(CO)R_3$  group, and the other one is -OH or  $-O(CO)R_3$ , or R<sub>1</sub> is =O and R<sub>2</sub> is H, wherein R<sub>3</sub> is a saturated or unsaturated acyclic hydrocarbon group having from 1 to about 20 carbon atoms, or  $-(CH_2)_mR_4$  wherein m is 0 or an integer of from 1 to 10, and R<sub>4</sub> is cycloalkyl radical, having from three to seven

carbon atoms, or a hydrocarbyl aryl or heteroaryl radical, or a pharmacologically acceptable acid addition salt thereof.

2. The composition of claim 1, wherein said prostaglandin based compound is either [(2-hydroxy-1-hydroxymethyl)ethyl]-9-oxo-11,15-dihydroxy-17-phenyl-18, 19, 20-trinor-prosta-5Z, 13E-dien-1-oate or 17-phenyl trinor prostaglandin E2 serinol amide.

3. The composition of claim 1, further comprising a stabilizing agent.

4. The composition of claim 3, wherein said stabilizing agent is a cyclodextrin.

5. The composition of claim 4, wherein said cyclodextrin is a selected from the group consisting of  $\alpha$ -cyclodextrin,  $\beta$ -cyclodextrin, a  $\gamma$ -cyclodextrin, 2-hydroxypropyl-alpha-cyclodextrin, 2-hydroxypropyl-beta-cyclodextrin, sulfobutyl ether-beta-cyclodextrin, and 2,6-dimethyl-beta cyclodextrin.

6. The composition of claim 3, wherein said stabilizing agent is dextran, dextrin, or pullulan.

7. A liposome comprising the composition of claim 1.

8. The liposome of claim 7, wherein said liposome comprises a phospholipid.

9. The liposome of claim 8, wherein said liposome further comprises retinyl palmitate, ascorbyl palmitate, or tocopheryl acetate.

10. The composition of claim 1, wherein said composition further comprises an alkyl benzoate.



11. The composition of claim 10, wherein said prostaglandin based compound and alkyl benzoate are contacted with an alcohol prior to formulation of the composition.

12. The composition of claim 10, wherein said prostaglandin based compound is provided admixed with said alkyl benzoate.

13. The composition of claim 12, wherein said alkyl benzoate is C<sub>12-15</sub> alkyl benzoate (Cetiol AB ®) or FINSOLV®TN-O.

14. The composition of claim 1, wherein said composition further comprises a preservative.

15. The composition of claim 1, wherein said composition further comprises a moisturizing agent.

16. A method of enhancing the appearance of at least one property of a subject's hair selected from the group consisting of: luster, sheen, brilliance, gloss, glow, shine, patina, length, thickness, and density; the method comprising contacting a portion of skin of a subject with the composition of claim 1, wherein said skin is associated with hair follicles and said contacting results in the enhancement of the appearance of the at least one property of the hair of the subject.

17. The method of claim 16, wherein the skin to be contacted is selected from the group consisting of skin associated with an eyelash, skin associated with an eyebrow, skin associated with a scalp, and skin associated with a face of the subject.

18. The method of claim 16, wherein said composition is formulated as an aqueous solution, an ointment, a liniments, a cream, a lotion, a paste, jelly, a shampoo, a rinse, a conditioner, an aerosol, or a spray.

19. The method of claim 16, wherein said contacting is performed at least once a day.
20. The method of claim 19, wherein said contacting is performed for at least 3 months.
21. A kit, the kit comprising one or more of the composition of claim 1, a suitable container for storing the composition, packaging, and directions for using the composition.

# INTERNATIONAL SEARCH REPORT

International application No  
PCT/US2009/043850

**A. CLASSIFICATION OF SUBJECT MATTER**  
INV. A61K8/365 A61Q5/00

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
A61K A61Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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A	WO 03/066008 A1 (ALLERGAN INC [US]) 14 August 2003 (2003-08-14) claims; examples & US 2003/147823 A1 (WOODWARD DAVID F [US] ET AL) 7 August 2003 (2003-08-07)	1-21
A	WO 01/74307 A2 (PROCTER & GAMBLE [US]) 11 October 2001 (2001-10-11) claims; examples ----- -/-	1-21



Further documents are listed in the continuation of Box C.



See patent family annex.

\* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
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- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
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Date of the actual completion of the international search

3 September 2009

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18/09/2009

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## INTERNATIONAL SEARCH REPORT

International application No

PCT/US2009/043850

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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L	Anonymous: "17-phenyl trinor Prostaglandin E2 serinol amide Catalog N° 10004238" Cayman Chemical, Ann Arbor, USA, Cayman Chemical Product Information XP002542046 Retrieved from the Internet: URL: <a href="http://www.caymanchem.com/pdfs/10004238.pdf">http://www.caymanchem.com/pdfs/10004238.pdf</a> [retrieved on 2009-08-19] the whole document	

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International application No.

PCT/US2009/043850

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